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Biphasic pleural mesothelioma in a electrician working in a railway company: case report and current trends in mesotheliomas in Italy

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ABSTRACT. **Background:** ***Mesothelioma is an aggressive tumour that can involve the pleura, the peritoneum, and sometimes other*** **mesothelia,** ***such as the pericardium and the*** **tunica vaginalis testis.** ***Scientific communities have known for a long time the causal correlation between exposure to asbestos (work related or not) and the onset of the disease (in 75% - 90% of cases) and the increasing number of asbestos-correlated mesotheliomas expected in the next years.*** **Case presentation:** ***The authors present the case of an electrician, 66-year-old man, died for pleural mesothelioma, working in Palermo in the company of the Italian Railways for a period of about 20 years, exposed to asbestos. Frequently he disassembled and reassembled the ceiling lights in the train carriages and worked in the same workplace where it was made the asbestos removal from train carriages. The autopsy showed a biphasic pleural mesothelioma, with mainly polymorphic desmoplastic-sarcomatous aspects, infiltrating the lung parenchyma, with areas of septal fibrosis and multiple outbreaks of pneumonia and edema.*** **Conclusions:** ***It is fundamental to know workers' risks to formulate a correct etiopathogenetic diagnosis, as in this presented case, not apparently in connection with asbestos (electrician worker). Because of the long latency in the genesis of mesothelioma after asbestos exposure (both because of the work and environmental pollution), it is considered appropriate to increase in Italy the activities of the regional centres of the Health System dedicated to health promotion and health surveillance of the former exposed to asbestos, created and active, unfortunately, only in some regions of our Country.***

Key words: *biphasic mesothelioma, asbestos, work-related disease, autopsy.*

RIASSUNTO. **Mesotelioma pleurico bifasico in un elettricista in servizio presso una azienda ferroviaria: descrizione di un caso clinico e attuale andamento dei mesoteliomi in Italia.** **Il mesotelioma è un tumore aggressivo che può coinvolgere la pleura, il peritoneo e talvolta altri mesoteli, come il pericardio e la tunica vaginale del testicolo. Le comunità scientifiche conoscono da molto tempo la correlazione causale tra l'esposizione all'amianto (correlata al lavoro o meno) e l'insorgenza della malattia (nel 75% - 90% dei casi) e il crescente numero di mesoteliomi correlati all'amianto attesi nella prossima anni.** ***Presentazione del caso:*** **Gli autori presentano il caso di un elettricista di 66 anni, deceduto per mesotelioma pleurico, che aveva svolto la sua mansione a Palermo nella compagnia delle Ferrovie italiane per un periodo di circa 20 anni, esposto all'amianto, adibito al montaggio e smontaggio delle plafoniere dei vagoni ferroviari, nello stesso ambiente ove avveniva la rimozione dell'amianto dai vagoni stessi. L'autopsia ha mostrato un mesotelioma pleurico bifasico, con aspetti prevalentemente desmoplastico-**

Introduction

Malignant pleural mesothelioma is an aggressive tumour and the number of cases increases constantly. The interest in this disease comes from many employment implications, in addition to the forensic and pathological aspects.

Scientific community highlighted since long time a causal correlation between exposure to asbestos (work related or not) and the onset of the disease (in 75% -90% of cases) (1-2).

In 1999 Peto J and other scientists predicted that for the period 1995-2029 the number of deaths due to mesothelioma in Western Europe each year would be almost double over the next 20 years, from 5,000 in 1998 to about 9,000 around 2018, and then would decline, with a total of about a quarter of a million deaths over the next 35 years (3). In Italy it was estimated a peak between 2015 and 2019 with 940 new cases per year (4).

For a long time it was estimated that there would be a peak with about 800 mesothelioma annual deaths in the period 2012-2024, increasing among males in Western Europe. Moreover, Italy, together with Greece and former Soviet Union countries, was also an asbestos producer in Europe, unlike other European countries that almost exclusively used imported material (5)

Although in Italy since 1992 is in force by law the prohibition of extraction, import, export, marketing and production of asbestos products, or products containing asbestos, there are currently still working categories exposed to this carcinogen in our Country (6). They are asbestos removal workers from architectural contexts (for example: roofs of industrial buildings, chimneys, containers for water) or from means of transportation, such as train carriages. Furthermore, for their long latency, we expect the emergence of new cases of mesotheliomas in those who were exposed to asbestos even some decades ago because of work done (7).

In Italy, before 1992, containment measures in some workplaces had already been introduced in the mid-1970s and limitations to the use of crocidolite were imposed in 1986, because in a lot of different Italian industrial and manufacturing sectors the situation was particularly alarming, as shown by incidence of and mortality from

sarcomatosi polimorfici, infiltranti il parenchima polmonare, con aree di fibrosi del setto e focolai multipli di polmonite ed edema. *Conclusioni:* È fondamentale conoscere i rischi dei lavoratori per formulare una corretta diagnosi eziopatogenetica, come in questo caso presentato, non apparentemente in relazione all'amianto, in base alla mansione svolta (operaio elettricista). A causa della lunga latenza nella genesi del mesotelioma dopo esposizione all'amianto (professionale e non), si ritiene opportuno aumentare in Italia le attività dei centri regionali del Sistema Sanitario dedicati alla promozione della salute e alla sorveglianza sanitaria di il primo esposto all'amianto, creati e attivi, purtroppo, solo in alcune regioni del nostro Paese.

Parole chiave: mesotelioma bifasico, asbesto, malattia lavoro-correlata, autopsia.

mesothelioma, which in some parts of Italy were among the highest in the world (5, 8)

The forecasts were founded if, in more recent times, the incidence standardized rate of pleural malignant MM by Italian National Mesothelioma Register (ReNaM) was 3.64 and 1.32 per 100,000 person/years in 2011 in men and women respectively with 1,428 (1,035 in men and 393 in women) recorded incident cases [V ReNaM Report]. Mortality rates for MM in 2011 were 2.74 and 0.83 in men and women with 1107 deaths, 786 and 321 respectively (9-10).

Recent cohort studies confirm the old predictions, also trying to bring out even the motivations of deaths due to an unspecified disease and clarify the determinism of other pathologies asbestos related and the specificity of illness in the female gender (11).

Moreover, recent studies carried out on various cohorts of Italian workers confirm that exposure to asbestos also leads to a long latency increase in the risk of cancer of the lung and ovary, as well as of the pleura and the peritoneum (12).

The anatomical-pathological diagnosis of mesothelioma can be difficult because of a particular characteristic which distinguishes it from many other neoplasms, namely its histological polymorphism.

In pleural and peritoneal cavities, in addition to mesothelioma, most often we can observe metastasis of primary tumours, which may be clinically silent, located in distant organs; so the differential diagnosis is very challenging.

According to recent international rules shared by pathologists, a reliable diagnosis of mesothelioma can be formulated only after histological examination performed on abundant material, at least 10 grams of anatomical tissue (according to Cotes and Steel), with an extremely accurate examination of the main organs and systems (by autopsy or clinical-instrumental exams), in order to exclude every other possible primary tumour (13).

More recent diagnostic criteria in the specific diagnosis are expressed by several Guidelines for pathologic diagnosis of malignant mesothelioma and recommendations (14-16).

Epithelial mesothelioma is the most common histological type (50-75%), followed by biphasic type (25-30%) and the sarcomatoid type (15-20%) (17).

Considering its unusual occurrence, we describe a case of biphasic mesothelioma, with mainly polymorphic desmoplastic-sarcomatous aspects, found at autopsy of a worker exposed to asbestos for many years.

Case Report

An autopsy was performed on a 66-year-old man in the Institute of Forensic Medicine of Palermo; he worked as an electrician in Palermo in the company of the Italian Railways for a period of about 20 years. In order to carry out its duties, frequently he disassembled and reassembled the ceiling lights in the train carriages. His work took place in the same workplace where it was made the asbestos removal from train carriages, with a consequent dispersion of asbestos fibers in the air. No direct information is available on the asbestos fiber type involved in this exposure.

Vacuum cleaners and ventilators were missing, as well as he proclaimed in medico-legal contest when, after clinical diagnosis of mesothelioma, he complained of having an occupational disease. He claimed that, like his fellow workers, usually did not use personal protective equipment, not washed frequently work overall and also said that the employer had not provided workers with training and specific information on the risk they were taking for their health, working with asbestos. He also reported that in the last year of his work, after medical examination, he had been exempted from his work task and moved into an office.

In physiological history claimed to have smoked about 20 cigarettes a day since he was 15 until he was 54 years of age, when he had a heart attack (12 years before diagnosis and subsequent death from mesothelioma). He contracted pleural tumour 36 years after first professional exposure to asbestos and six months after this diagnosis the subject died. The CT imaging of the chest, performed during hospitalization, two months before death, is shown in Figure 1 and 2. At autopsy, the left lung appeared completely wrapped by a newly-formed hard-fibrous mass "in armor", originating from the visceral pleura, having a greyish-white colour, tight to the ipsilateral costal wall and fibrous pericardium, and obliterating pleural cavity (Figure 3).

Following the removal in full of heart and lungs, we proceeded with the macroscopic evaluation of the two lungs. This operation was particularly difficult because of adhesions between the lungs and costal walls, of diffuse type on the left and with synechiae on the right and for the tenacious adhesions between the lungs and the diaphragm (Figure 4).

The right lung was regular in shape and volume, pale in the front side, with areas of anthracosis, while the left lung appeared woody and with hard-consistency, when cut, with a subversion of structure, caused by tumour infiltrating parenchymal tissue (Figure 5).

The histological exam confirmed the diagnosis of malignant biphasic mesothelioma, with mainly polymorphic desmoplastic-sarcomatous aspects, infiltrating the lung parenchyma, with areas of septal fibrosis and multiple outbreaks of pneumonia and edema (Figure 6).

In the context of the neoplastic tissue were advised, even, neoplastic vascular infiltrations and fibres of asbestos (Figure 7).

Figura 1. ***High-resolution axial un-enhanced CT image (lung windowing) highlighting multiple nodular pleural thickening (yellow arrow) and centrolobular (magnified)***

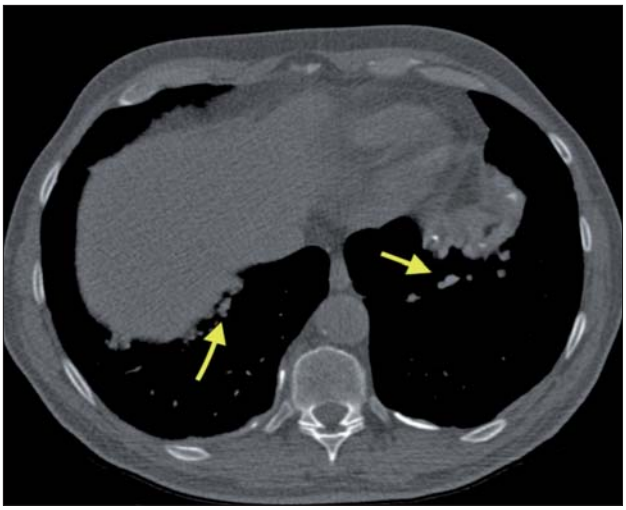

Figura 2. ***Unenhanced High Resolution CT showing multiple nodular thickening of the diaphragmatic pleura (yellow arrow)***

Figura 3. ***Left lung completely wrapped by a newly-formed hard-fibrous mass "in armor", originating from the visceral pleura, having a grayish-white colour, tight to the ipsilateral costal wall and fibrous pericardium, and obliterating pleural cavity***

Discussion

The relationship between asbestos and mesothelioma first identified by Wagner et al. in South Africa, has now been documented all over the world (18). The average prevalence of mesothelioma in people with prolonged heavy exposure to asbestos is 2% to 3%, but has reached up to 10% in some series (19). The latency period is usually 20 years or longer (20).

Although few authors confirmed the synergistic role of smoking cigarettes with the asbestos in causing pleural mesothelioma, the International Agency for Research on Cancer (IARC) affirms that "…Malignant tumours arising in the pleural or peritoneal linings (diffuse malignant mesothelioma) have no association with tobacco smoking" (21-22).

Malignant mesothelioma is usually seen in older adults, although well-documented cases in younger individuals are on record (23). In some instances a familial clustering has been demonstrated (24).

In most instances the initial involvement is in the lower half of a hemithorax, but spread to the rest of the pleural cavity is the rule.

Grossly, the classical presentation is that of multiple grey or white ill-defined nodules in a diffusely thickened pleura. It is much rarer for it to present as a localized pleural mass (25). Pleural effusion is almost always present. Microscopically the main variants of malignant mesothelioma are the epithelioid mesothelioma, the spindle cell or sarcomatoid mesothelioma and the biphasic mesothelioma where the two components, epithelial and spindle cells co-exist, although it is rare to find a mesothelioma with an equal quantity ratio of the two types in a uniform distribution. More often a component prevails in an area and the other in another part of the same tumour.

They also include rarer histologies like the desmoplastic mesothelioma, the lymphohistiocytoid mesothelioma, the deciduoid mesothelioma, the squamous differentiated mesothelioma (pleural squamous cell carcinoma) and the small cell variant one.

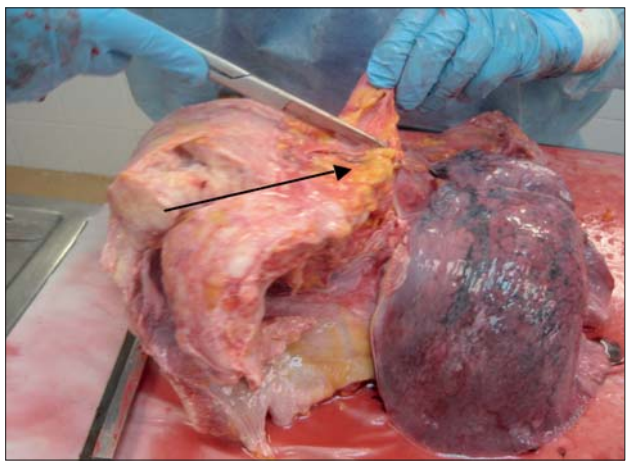

Figura 4. ***"En block" dissection of heart and lungs; macroscopic evaluation of the two lungs. Diffuse type on the left and with synechiae on the right and for the tenacious adhesions between the lungs and the diaphragm (arrow).***

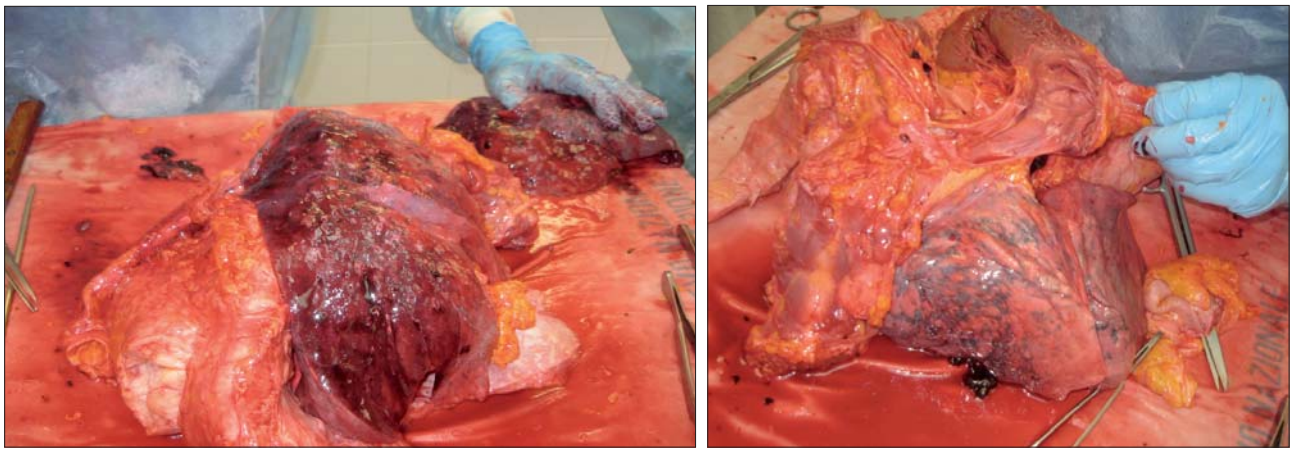

Figura 5. ***Right lung (regular shape and volume) pale in the front side, with areas of anthracosis; left lung with hard-consistency, with a subversion of structure, caused by tumour infiltrating parenchymal tissue***

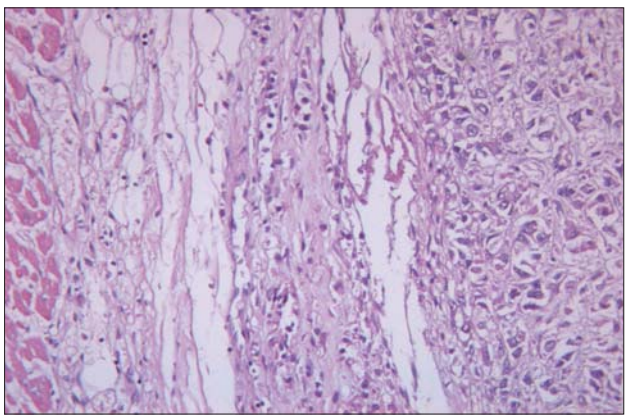

Figure 6. ***Histological stain of tissue lung: mainly polymorphic desmoplastic-sarcomatous aspects, infiltrating the lung parenchyma, with areas of septal fibrosis and multiple outbreaks of pneumonia and edema (H & H, 20 X magnification)***

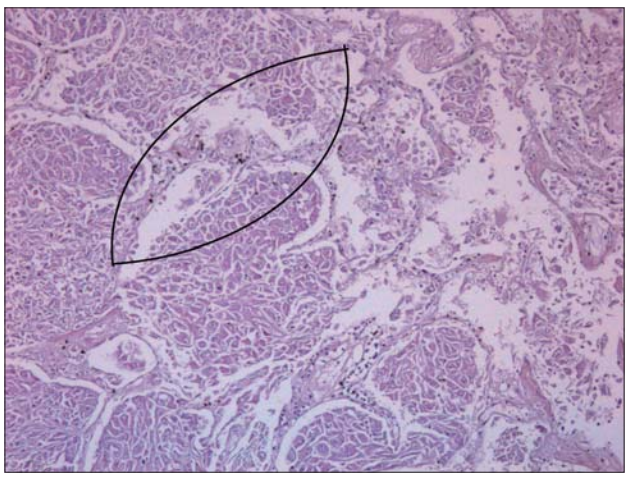

Figure 7. ***Neoplastic vascular infiltrations and fibres of asbestos in the context of the neoplastic tissue (H & H, 20 X magnification)***

The case came to our observation showed biphasic characteristics with the prevalence of polymorphic sarcomatous and desmoplastic aspects. It seems worthy of considering, also in medico legal perspective, the role of occupational exposure as a clear explanation of the causes of death (26). Noteworting, in the Italian registry of Mesotelioma, for 142 cases (15% of males and 23% of women) the first diagnosis was made at autopsy. Autopsy findings improved the diagnostic level of malignant mesothelioma (MM) in elderly subjects, for whom reliable data on past asbestos exposure is often lacking (27-28).

Also, in the view of educational objects, it seems appropriate to briefly refer to the histological features observed in the present case. As regards the epithelial component, also called epithelioid, it usually has a predominantly tubular or papillary or tubular-papillary architectural pattern, but can also occur in solid form (non-glandular) (29). The main differential diagnosis is with the more cellular types of solitary fibrous tumours of pleura, some of which may be malignant themselves. It also needs to be distinguished from areas of dense inflammatory fibrosis.

In Italy since 2002 exists the National Mesotheliomas Register (Renam), an epidemiological surveillance system of mesothelioma cases, defined by the Law 308/2002 (30).

The actual situation in Italy, specifically thousands of asbestos-related new diseases every year and hundreds of deaths, is a consequence of its use made from 1945 to 1992. In that period in Italy were used 3,748,550 tons of raw asbestos produced in Italian territory and 1,900,885 tons of raw asbestos imported from foreign Countries.

The 5th Renam Report just released by Inail (National Institute for Insurance Against Accidents at Work) reports data concerning mesothelioma cases detected by Cor (regional operational Centres), and diagnosed from 1993 to 2012. In the twenty year period considered, were detected by the network of centres 21,463 mesothelioma cases: 93% originated from the pleura, 6.5% from the peritoneum and then 65 cases from the pericardium and 51 cases originated from the tunica vaginalis of the testis (31).

The mean age at diagnosis was 69.2 years, without appreciable differences by gender (68.8 in men and 70.2 years in women). The gender ratio (male cases for each case of feminine gender: M/F) is equal to 2.5. 71.6% of

the 21,463 patients were male. The percentage of women is 27.5% for pleural mesotheliomas and 31.4% and 41.3% respectively for cases of pericardial and peritoneal mesotheliomas.

The exposures were known in 16,511 cases (76.9%) and, among these, 69.5% had occupational exposure (certain, probable, possible), 4.8% at home, 4.2% environmental, 1.6% for a leisure activity outside work or hobbies. In 20% of cases the exposure was unknown. The proportion of cases of mesothelioma with certain and known exposure is 80.1% on the entire dataset. Considering the entire observation period (1993-2012) and the only persons affected by disease for professional reasons, the sectors most affected were the construction industry (15.2% of total cases), heavy industry, particularly the metal industry (8.3%), metallurgy (3.9%) and manufacture of metal products (5.7%); the shipyards (6.7%), the asbestos-cement industry (3.1%). Other activities are extremely diverse and fractioned, with the presence of numerous production areas where the exposure took place in the presence of the material in the workplace and not for direct use (31).

The causal link between occupational exposure to asbestos in the railway carriages production sector and the onset of pleural mesothelioma has been known for decades, as described by various reports, including Italian ones, reported in the scientific literature (32-35).

Because of the long latency in the genesis of mesothelioma after asbestos exposure (at work and not), it is considered appropriate to increase in Italy the activities of the regional centres of the Health System dedicated to health promotion and health surveillance of the former exposed to asbestos, created and active unfortunately only in some regions of our country (36).

This could be useful in bringing out all cases of diseases in work sectors different than those traditionally considered as being at risk, such as school teachers. In this regard, we recall how school buildings in Italy are often very old and not compliant with laws that protect workers' health and safety, also due to lack of economic funds. Clinical cases in this regard have already been described (37-38).

It would also be important to investigate in which other "non-traditional" working sectors asbestos was used, in order to monitor in these centers of reference these other workers, who are no longer active. In fact, it happens to find mesotheliomas in atypical workers for this risk, such as, for example, furniture makers or cellars (39-40).

Conclusions

In light of the long latency of the onset of mesotheliomas in workers and citizens exposed to asbestos, both occupational medicine and public health will have to deal with these pathologies for a long time. In some regions of Italy many projects have been planned for the disposal of asbestos-containing waste dispersed throughout the territory, unfortunately not all already operational, with consequent environmental contamination still at the present time.

The case reported here, like others described in the literature, must always alert the occupational physicians, since not only the task (electrician, furniture maker, teacher, cellarman), but also and above all the places where the work is carried out, must presuppose a specific exposure, with the subsequent determinism of related diseases.

In this regard, the figure of the occupational physician could be decisive in the work of detection of all the tasks so far not included among those traditionally at risk of exposure to asbestos, collaborating effectively with the regional reference centers for monitoring of mesotheliomas and all other asbestos-related diseases.

It would also be interesting to find out if in the female sex occupational exposure plays a fundamental role and identify in which circumstances 20% of the cases reported by the RENAM with unknown exposure have come into contact with asbestos. Therefore the work of researchers on these issues in the next years will have to be constant in shedding light on what is still misunderstood.

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